PATENT SPECIFICATION

1,043,158

NO DRAWINGS

1,043,158

Date of Application and filing Complete Specification: May 28, 1963.
No. 21348/63.
Application made in Switzerland (No. 6886) on June 7, 1962.
Application made in Switzerland (No. 1455) on Feb. 6, 1963.
Application made in Switzerland (No. 5377) on April 30, 1963.
Complete Specification Published: Sept. 21, 1966.

Index at acceptance:—C2 C(1E3K3, 1E3K6, 1E5K3, 1E5K4, 1E5K6, 1E6K3, 1E6K6, 1G5A, 1G5B, 1G6B3, 1G6B4, 1G6B6, 1Q1A, 1Q4, 1Q6B1, 1Q6B2, 1Q6C, 1Q8A, 1Q9B, 1Q9D2, 1Q9F2, 1Q11D, 1Q11J, 3A13A3A4, 3A13A3B3, 3A13A3C, 3A13A3F3, B4A2, B4K, B4M)

Int. Cl.:—C 07 d 29/02

The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act 1949 are:— ERNST JUCKER, Steinweg 28, Ettingen, Baselland, Switzerland and ANTON EBNOTHER, Florastrasse 3, Reinach, Baselland, Switzerland; both Swiss citizens.

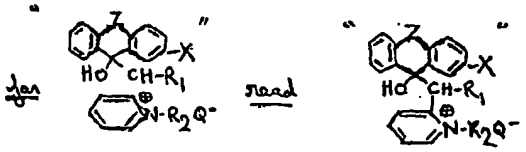
COMPLETE SPECIFICATION

Improvements in or relating to Piperidylalkidene-5H-Dibenzo(a,d)Cycloheptenes

ERRATA

SPECIFICATION No. 1,043,158
Amendment No. 1

Page 2, line 41,



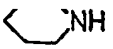
Page 3, line 122, *for* "taken" *read* "shaken"
Page 4, line 12, *for* "methyl" *read* "methylene"
Page 6, line 76, *for* "be" *read* "by"
Page 9, line 7, *for* "methyl" *read* "ethyl"

THE PATENT OFFICE
7th November 1966

(C_1—C_4) radical and
R_2 a hydrogen atom or an alkyl (C_1—C_4), alkenyl (C_2—C_4) or 2-hydroxyalkyl (C_2 or C_3) radical,

and salts and quaternary compounds of these.

[*Pr*]



VII

in which Z, X and R_1 have the above significance.

1,043,158

PATENT SPECIFICATION

NO DRAWINGS

1,043,158

Date of Application and filing Complete Specification: May 28, 1963.
No. 21348/63.
Application made in Switzerland (No. 6886) on June 7, 1962.
Application made in Switzerland (No. 1455) on Feb. 6, 1963.
Application made in Switzerland (No. 5377) on April 30, 1963.
Complete Specification Published: Sept. 21, 1966.

Index at acceptance:—C2 C(1E3K3, 1E3K6, 1E5K3, 1E5K4, 1E5K6, 1E6K3, 1E6K6, 1G5A, 1G5B, 1G6B3, 1G6B4, 1G6B6, 1Q1A, 1Q4, 1Q6B1, 1Q6B2, 1Q6C, 1Q8A, 1Q9B, 1Q9D2, 1Q9F2, 1Q11D, 1Q11J, 3A13A3A4, 3A13A3B3, 3A13A3C, 3A13A3F3, B4A2, B4K, B4M)

Int. Cl.:—C 07 d 29/02

The inventors of this invention in the sense of being the devisers thereof within the meaning of Section 16 of the Patents Act 1949 are:— ERNST JUCKER, Steinweg 28, Ettingen, Baselland, Switzerland and ANTON EBNOTHER, Florastrasse 3, Reinach, Baselland, Switzerland; both Swiss citizens.

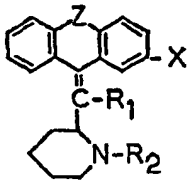
COMPLETE SPECIFICATION

Improvements in or relating to Piperidylalkidene-5H-Dibenzo(a,d)Cycloheptenes

We, SANDOZ PATENTS LIMITED of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new tricyclic organic compounds and to processes for their production.

The present invention provides 5 - [1′ - (piperidyl - 2″) - alkylidene] - 5H - dibenzo[a,d]cycloheptenes of the formula I,

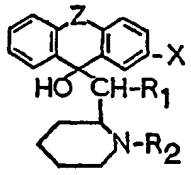


I

in which Z denotes a $-CH_2-CH_2-$ or a $-CH=CH-$ radical,
X denotes a hydrogen, fluorine, chlorine or bromine atom,
R_1 a hydrogen atom or an alkyl (C_1—C_4) radical and
R_2 a hydrogen atom or an alkyl (C_1—C_4), alkenyl (C_2—C_4) or 2 - hydroxyalkyl (C_2 or C_3) radical,
and salts and quaternary compounds of these.

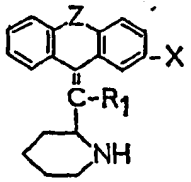
[*Pr*]

The invention also provides a process for the production of the compounds I, which comprises heating with a strong acid or acid anhydride to split off the elements of water from the corresponding 5 - [1′ - (piperidyl - 2″) - alkyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol of the formula II,



II

in which Z, X, R_1 and R_2 have the above significance, or substituting the radical R_2— when this is other than a hydrogen atom— directly on the nitrogen atom of a compound of the formula VII,



VII

in which Z, X and R_1 have the above significance.

The resulting compounds of formula I may then be converted in manner known *per se* to their acid addition salts or quaternary compounds and/or be separated into their cis- and trans-isomeric forms.

The substitution of compounds of the formula VII may be achieved, when R_2 is the above alkyl or alkenyl radical, for example, (i) by direct alkylation with an alkyl halide of the formula VIII,

$$R_2'Hal \qquad VIII$$

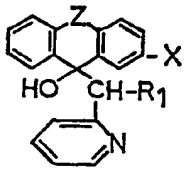
in which R_2' denotes an alkyl (C_1—C_4) or alkenyl (C_2—C_4) radical in the presence of a basic catalyst (e.g. sodamide) or (ii) by acylation with a reactive derivative of an acid of the formula IX,

$$R_3COOH \qquad IX$$

in which R_3 is an alkyl ar alkenyl radical having one —CH_2-radical less than R_2,

followed by reduction with lithium aluminium hydride or diborane of the resulting acid amide, or (iii), when R_2 is a methyl radical by reductive alkylation with formaldehyde and formic acid. Compounds of the formula I, in which R_2 denotes a 2-hydroxyalkyl (C_2 or C_3) radical, may be produced from the compound of the formula VII by reaction with a corresponding epoxide.

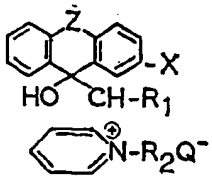
The starting materials of formula II, which are also new, may be produced, when R_2 is an alkyl (C_1—C_4) or 2-hydroxyalkyl (C_2 or C_3) radical, from a compound of the formula III,



III

in which Z, X and R_1 have the above significance,

by quaternization with a suitable alkylating agent and reduction as described below of the resulting compound of formula IV,



IV

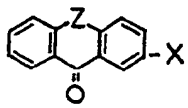
in which Z, X, R_1 and R_2 have the above significance, and

Q^- denotes the anion corresponding to the alkylating agent which is used.

When a compound II, wherein R_2 = H, is required, the corresponding compound III is reduced directly as described below.

Esters of sulphuric acid or sulphonic acid (e.g. dimethyl sulphate, *p*-toluenesulphonic acid methyl ester) or alkyl halides are preferably used for quaternization. Reduction of the quaternary pyridinium compound to the corresponding piperidyl compound is carried out catalytically (using a platinum catalyst or Raney nickel), while the direct reduction of the pyridine ring of a compound III may likewise be effected catalytically or with sodium in absolute ethanol. Of the compounds III, 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene - 5 - ol is already known; the others are new.

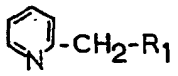
In general, the compounds III may be produced by reacting a compound of the formula V,



V

in which Z and X have the above significance,

with a sodium or lithium derivative of a compound having the formula VI,



VI

in which R_1 has the above significance

and hydrolysing the resulting complex compound. The sodium and lithium compounds are produced by methods known *per se* and are suitably used in the form of a solution in an absolute solvent.

The compounds of the formula V, in which X denotes hydrogen or a chlorine atom, are already known.

The compounds of the formula V, in which X denotes fluorine or bromine are new and may be produced by the following process which also constitutes part of the invention: The corresponding *p* - halogeno - benzalphthalide is reduced with hydriodic acid and red phosphorus to give the corresponding *o* - (*p* - halogenophenethyl) - benzoic acid which is intramolecularly cyclized to

the corresponding 3 - halogeno - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - one, e.g. by heating with polyphosphoric acid.

In order to synthesize the desired compound of the formula I, the corresponding compound of the formula V is preferably used as starting material, although a compound in which Z denotes a $-CH_2-CH_2-$ radical can be converted to a compound in which Z denotes a $-CH=CH-$ radical, and vice-versa, by methods known *per se*, in an additional process step. The compounds of the invention are crystalline or of oily consistency at room temperature and form stable salts, which crystallize at room temperature, with inorganic or organic acids, e.g. hydrochloric, hydrobromic, sulphuric, citric, tartaric, succinic, maleic, malic, acetic, benzoic, hexahydrobenzoic, methanesulphonic, fumaric, gallic and hydriodic acid.

The compounds of the formula I have valuable pharmacodynamic properties which cannot be predicted from their constitution. Thus, some of the compounds of the invention have a strong neuroleptic action which manifests itself, e.g. by adrenalin antagonism and narcosis potentiation and especially by an outstanding and very specific antiemotional action. It was not to be expected that this property, which has hitherto only been known to such an extent in compounds having 3 carbon atoms between the tricyclic nucleus and the nitrogen atom of the side-chain, would be possessed by compounds having only two carbon atoms between the tricyclic nucleus and the nitrogen atom of the side-chain. In the dosages required to produce a neuroplegic effect the toxicity of the compounds is very low. The compounds I therefore have properties useful in neuroplegic agents or antiemotional agents, for example for the treatment of stress conditions; the compound 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene is especially useful in this respect. The exact pharmacological activity of each compound I depends on the nature of the symbols Z, X, R_1 and R_2.

The compounds I may be worked up in the form of pharmaceutical preparations. These contain the compound of the invention in admixture with an organic or inorganic carrier which is suitable for enteral, parenteral or local application and which does not react with the compounds I, e.g. gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, benzyl alcohols, gum arabic, polyalkylene glycols, petroleum jelly, cholesterol or other known pharmaceutical carriers. The pharmaceutical preparations may, for example, be in the form of tablets, dragees, powders, creams, suppositories or in liquid form as solutions, suspensions or emulsions; they may, if desired, be sterilized and/or contain adjuvants such as preserving agents, stabilizers, wetting agents or emulsifiers, or other therapeutically active substances.

The invention thus further provides pharmaceutical preparations containing, in addition to a physiologically acceptable carrier, a compound I above and/or a physiologically acceptable acid addition salt or quaternary ammonium compound thereof.

In the following non-limitative Examples, all temperatures are indicated in degrees Centigrade. Melting points are uncorrected.

EXAMPLE 1:

5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d] cycloheptene

a) 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol

9.5g of 2-methylpyridine are added dropwise to a lithium phenyl solution, prepared from 1.39g of lithium and 15.7g of bromobenzene in 75 ml of ether, the solution is then boiled for 30 minutes under reflux, cooled and then a solution of 10.4g of 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - one (m.p. 34—35°) in 25 ml of ether is added dropwise at room temperature.

Stirring is then carried out for one hour at room temperature, the solution then poured into 200 ml of 10% aqueous ammonium chloride solution and shaken out repeatedly with methylene chloride. After drying over sodium sulphate, the solvent is removed by evaporation and the residue recrystallized from methanol. M.p. = 113—115°.

b) 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol

14.3g of 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol, 7.15g of dimethyl sulphate and 70 ml of acetone are boiled for two hours under reflux. It is left to cool, the 5 - [(1' - methyl - pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol - methyl sulphate filtered off and dried in a vacuum. The quternary salt is then dissolved in 150 ml of methanol and shaken with hydrogen at room temperature, after adding 0.2g of platinum oxide, until the calculated amount has been taken up. The catalyst is filtered off, the solution reduced in volume by evaporation, the residue taken with dilute sodium hydroxide solution and methylene chloride, the methylene chloride layer dried over sodium sulphate and reduced in volume by evaporation and the residue crystallized from methanol. M.p. = 124—125°.

c) 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene

9g of 5 - [(1' - methyl - piperidyl - 2') - methyl] - dibenzo[a,d]cyclohepten - 5 - ol, 90 ml of glacial acetic acid and 36 ml of concentrated hydrochloric acid are boiled under reflux for one hour. It is then reduced in volume in a vacuum, the residue dissolved in water, rendered alkaline with sodium hydroxide solution and the base which has separated is taken up in methyl chloride. After drying over sodium sulphate and evaporating the solvent, the residue is recrystallized from hexane. M.p. = 109—110°.

EXAMPLE 2:

3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene

a) 3 - chloro - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol

This compound is produced in a manner similar to that described in Example 1 from 3 - chloro - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - one and 2-methylpyridine. M.p. = 116—117° from methanol.

b) 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol

This compound is produced in a manner similar to that described in Example 1 from 3 - chloro - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol. M.p. 139—145°.

c) 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene

7.8g of 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol are boiled under reflux for one hour with 75 ml of glacial acetic acid and 30 ml of concentrated hydrochloric acid. It is then reduced in volume in a vacuum, the residue shaken with dilute sodium hydroxide solution and methylene chloride, the methylene chloride layer dried over potassium carbonate and reduced in volume by evaporation. The mixture of cis-trans isomers of the compound quoted in the title crystallizes after some time from the solution of the residue in petroleum ether. On recrystallizing from ethanol, only the α-isomer crystallizes out; this melts at 138—139° after twice recrystallizing from hexane. The ethanol mother liquor is reduced in volume by evaporation and the residue dissolved in acetone. A fraction crystallizes out, markedly enriched in the β-isomer. This latter is obtained in practically pure form after repeated crystallization from acetone. M.p. = 113—116°.

EXAMPLE 3:

5 - [(1' - methyl - piperidyl - 2') - methylene] - 5H - dibenzo[a,d]cycloheptene

a) 5 - [(pyridyl - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol

The solution of 4.65g of 2 - methyl - pyridine in 10 ml of absolute tetrahydrofuran is first added dropwise to a sodium amide suspension, prepared from 2.3g of sodium and 100 ml of liquid ammonia and followed by the solution of 10.3g of 5H - dibenzo[a,d]cyclohepten - 5 - one (m.p. 89—90°) in 15 ml of absolute tetrahydrofuran. It is stirred for two hours at the boiling temperature of liquid ammonia and the reaction mixture then poured into a solution of 5.5g of ammonium chloride in 100 ml of liquid ammonia. The ammonia is then allowed to evaporate and the residue poured into water. The precipitated substance is filtered off, dried and recrystallized from methanol. M.p. = 107—108°.

b) 5 - [(1' - methyl - piperidyl - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol

14.9g of 5 - [(pyridyl - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol, 7.5g of dimethyl sulphate and 40 ml of acetone are boiled under reflux for two hours. 80 ml of ether are then added and the resinous precipitate which has formed is separated by decanting. The precipitate is washed twice with ether and dried. The frothy quaternary salt is then dissolved in 150 ml of methanol and the solution shaken with hydrogen at room temperature, after adding 0.3g of platinum oxide, until the calculated amount of hydrogen has been taken up. The catalyst is then removed by filtering, the solution evaporated in a vacuum, the residue shaken with dilute sodium hydroxide solution and methylene chloride, the methylene chloride layer dried over potassium carbonate and reduced in volume by evaporation. The residue is recrystallized from acetone. M.p. = 152—153°.

c) 5 - [(1' - methyl - piperidyl - 2') - methylene] - 5H - dibenzo[a,d]cycloheptene

7.5g of 5 - [(1' - methyl - piperidyl - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol, 75 ml of glacial acetic and 30 ml of concentrated hydrochloric acid are boiled under reflux for 1 hour. After evaporating in a vacuum, the residue is shaken with dilute sodium hydroxide and methylene chloride and the methylene chloride layer reduced in volume by evaporation, after drying over

potassium carbonate. The residue is triturated with petroleum ether. Undissolved, resin-like flakes are filtered off and the solution is reduced in volume once more. The residue is dissolved in acetone and acidified with a solution of hydrogen chloride in absolute ether, whereupon the hydrochloride of the compound quoted in the title crystallizes. M.p.: 252—254° (decomposition). It crystallizes from ethanol with one alcohol of crystallization. M.p. 130—132°.

EXAMPLE 4:

3 - fluoro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo [a,d]cycloheptene

a) *o* - (*p* - fluorophenethyl) - benzoic acid

150g of *p* - fluorobenzal phthalide, 320 ml of hydroiodic acid (d = 1.7) and 55g of red phosphorus are boiled under reflux for 15 hours. The reaction mixture is poured into one litre of water, the precipitated substance filtered off, washed with a little water and boiled for thirty minutes, while stirring, with 1/2 litre of concentrated ammonium hydroxide solution. On cooling filtering is carried out and the filtrate rendered Congo-acid with 20% hydrochloric acid. The precipitate of *o* - (*p* - fluorophenethyl) - benzoic acid is filtered off, dried and recrystallized from methanol. M.p. 132—133°.

b) 3 - fluoro - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - one

100g of *o* - (*p* - fluorophenethyl) - benzoic acid and 500g of polyphosphoric acid are heated to 170° for 3 hours. The reaction mixture is then poured into 2 litres of ice water, shaken out three times with methylene chloride, the methylene chloride extract washed with sodium carbonate solution and evaporated to dryness over magnesium sulphate. The residue is distilled in a high vacuum, whereupon the 3 - fluoro - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - one distils over at 163—164° at 0.1 mm Hg, as a faintly yellow oil.

c) 3 - fluoro - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - ol

9.5g of α-picoline are added to a lithium phenyl solution which is prepared from 1.39g of lithium and 15.7g of bromobenzene in 75 ml of ether. The solution is boiled under reflux for 30 minutes, cooled and the solution of 11.31g of 3 - fluoro - 10,11 - dihydro - 5H - dibenzo a,d cycloheptен - 5 - one in 25 ml of ether then added dropwise at room temperature. Stirring is carried out for one hour at room temperature, the reaction mixture is poured into 200 ml of 10% aqueous ammonium chloride solution and shaken out repeatedly with methylene chloride. After drying over sodium sulphate, the solvent is evaporated and the residue recrystallized from ethanol. M.p. of the pure 3 - fluoro - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - ol = 116—118°.

d) 3 - fluoro - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - ol

12g of 3 - fluoro - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptен - 5 - ol, 4.2g of dimethyl sulphate and 36 ml of acetone are boiled for 2½ hours under reflux. After allowing the solution to cool, the 3 - fluoro - 5 - [(1' - methyl - pyridinium - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - ol - methosulphate which crystallizes out is filtered and dried in a vacuum. The quaternary salt is then dissolved in 120 ml of methanol and the solution shaken with hydrogen at room temperature after adding 0.2g of platinum oxide, until the calculated amount of hydrogen has been taken up. The catalyst is filtered off, the solution reduced in volume by evaporation, the residue shaken with dilute sodium hydroxide solution and methylene chloride, the methylene chloride phase dried over sodium sulphate, then reduced in volume and the residue crystallized from ethanol. M.p. of the pure 3 - fluoro - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - ol: 145—147°.

e) 3 - fluoro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene

10g of 3 - fluoro - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptен - 5 - ol are boiled under reflux for one hour with 100 ml of glacial acetic acid and 40 ml of concentrated hydrochloric acid. The solution is then reduced in volume in a vacuum, the residue shaken out with dilute sodium hydroxide and methylene chloride, the methylene chloride phase dried over potassium carbonate and reduced in volume by evaporation. The partially crystallized residue is dissolved in 15 ml of ethanol, whereupon the α-isomer of the compound quoted in the title crystallizes. This melts at 126—128° after twice recrystallizing from hexane.

The alcohol mother liquor is reduced in volume by evaporation and the residue dissolved in petroleum ether. A mixture of isomers crystallizes, in which the β-isomer is markedly enriched. This latter is obtained in pure form by repeated recrystallization from acetone; its melts at 97—98.5°.

EXAMPLE 5:

3 - bromo - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene

a) *o* - (*p* - bromo - phenethyl) - benzoic acid

This compound is produced from *p* - bromo - benzalphthalide in a manner similar to that described in Example 4. M.p. = 126—127° from methanol.

b) 3 - bromo - 10,11 - dihydro - 5H - dibenzo [a,d]cyclohepten - 5 - one

This compound is produced from *o* - (*p* - bromophenethyl) - benzoic acid in a manner similar to that described in Example 4. M.p. = 78—80° from ethanol. B.p. = 180—190° at 0.1 mm Hg.

c) 3 - bromo - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]-cyclohepten - 5 - ol

This compound is produced from α-picoline and 3 - bromo - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - one in a manner similar to that described in Example 4. M.p. = 119—121° from ethanol.

d) 3 - bromo - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol

This compound is produced from 3 - bromo - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - ol in a manner similar to that described in Example 4. M.p. = 134—150° from ethanol (mixture of isomers).

e) 3 - bromo - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene

This compound is produced from 3 - bromo - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo-[a,d]cyclohepten - 5 - ol in a manner similar to that described in Example 4. The crude reaction product is dissolved in ethanol, whereupon the α-isomer crystallizes. M.p. = 133—134° after twice recrystallizing from ethanol.

The mother liquors are treated in ethanol with the calculated amount of naphthalene-1,5 - disulphonic acid to produce the neutral naphthalene - 1,5 - disulphonate, whereupon a mixture of the neutral α- and β - naphthalene - 1,5 - disulphonates crystallizes. M.p. = 220—235° after recrystallizing from methanol.

EXAMPLE 6:

3 - chloro - 5 - (2' - piperidyl - methylene) - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene

a) 3 - chloro - 5 - (2' - piperidyl - methyl) - 10,11 - dihydro - 5H dibenzo[a,d]cyclohepten - 5 - ol

15g of 3 - chloro - 5 - [(pyridyl - 2') - methyl] - 10,11 - dihydro - 5H - dibenzo-[a,d]cyclohepten - 5 - ol. in 100 ml of glacial acetic with 0.3g of platinum oxide are shaken with hydrogen at 6 atmospheres (gauge) at 60°. When no more hydrogen is taken up, the catalyst is filtered off and the filtrate reduced in volume by evaporation in a vacuum. The residue is dissolved in water, the solution rendered alkaline with sodium hydroxide solution, shaken out repeatedly with methylene chloride, the methylene chloride phase dried over magnesium sulphate and reduced in volume be evaporation. The frothy residue is dissolved in ethanol, whereupon small amounts of a more highly hydrogenated product crystallize. This product is filtered off and the filtrate acidified with an ethereal hydrogen chloride solution, whereupon the hydrochloride of an isomeric mixture of 3 - chloro - 5 - (2' - piperidyl - methyl) - 10,11 - dihydro - 5H - dibenzo-[a,d]cyclohepten - 5 - ol crystallizes. M.p. = 253—257° (decomposition) after recrystallization from ethanol.

b) 3 - chloro - 5 - (2' - piperidyl - methylene) - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene

40g of 3 - chloro - 5 - (2' - piperidyl - methyl) - 10,11 - dihydro - 5H - dibenzo-[a,d]cyclohepten - 5 - ol hydrochloride, 400 ml of glacial acetic and 160 ml of concentrated hydrochloric acid are boiled under reflux for one hour. It is then reduced in volume by evaporating in a vacuum, the residue is dissolved in water, made alkaline with sodium hydroxide solution and the base which precipitates is taken up in methylene chloride. After drying over potassium carbonate and evaporating the solvent, the residue is dissolved in methanol, whereupon the α-form of the compound quoted in the title crystallizes. It melts at 165—166° after twice recrystallizing from ethanol. The hydrochloride of the α-form melts at 240—245°, with decomposition, after crystallization from ethanol/ether.

The methanol mother liquor is acidified with ethereal hydrogen chloride and the crystallized hydrochloride twice recrystallized from methanol. The hydrochloride is thus obtained in the β-form; m.p. = 299—303° (decomposition). The β-base which is liberated from the hydrochloride melts at 125—127° after crystallization from acetone.

EXAMPLE 7:

α - isomer of 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene

6.5g of the α - isomer of 3 - chloro - 5 - (2' - piperidyl - methylene) - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, 5 ml of 98% formic acid and 2.5 ml of 40% formaldehyde solution are heated for 18 hours at 100°. It is then cooled, 22 ml of N hydrochloric acid are added, dissolving is effected by heating on a water-bath and the solution reduced on volume by evaporation in a vacuum. The residue is dissolved in water, the solution made alkaline with sodium hydroxide solution and the precipitated base taken up in methylene chloride. After drying over magnesium sulphate, the solution is reduced in volume and the residue dissolved in 10 ml of ethanol, whereupon the α - isomer of 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene crystallizes. M.p. = 138—139° on recrystallization from ethanol.

EXAMPLE 8:

α - 3 - chloro - 5 - [(1' - ethyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene

2.5 ml of triethylamine are added to a solution of 5g of α - 3 - chloro - 5 - (2' - piperidyl - methylene) - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene in 75 ml of methylene chloride, a solution of 1.25 ml of acetyl chloride in 5 ml of methylene chloride is then added dropwise at 20° and stirring carried out for 3 hours at room temperature. The solution is then shaken out three times with water, the organic phase dried over magnesium sulphate, reduced in volume by evaporation and the resinous residue dried in a vacuum. This is then dissolved in 50 ml of absolute tetrahydrofuran and a suspension of 750 mg of lithium aluminium hydride in 10 ml of tetrahydrofuran added to the solution at 20°. After stirring for one hour at room temperature, the solution is left to boil under reflux for a further two hours, then cooled down and saturated aqueous sodium sulphate solution slowly added dropwise until a precipitate is deposited. This is filtered off and boiled twice more with tetrahydrofuran. The united filtrates are reduced in volume by evaporating in a vacuum and the residue distilled in a bulb tube, whereupon the compound quoted in the title distils over as a colourless oil at 160—180° (air bath temperature) at 0.02 mm Hg.

5g of this crude oil are dissolved in 20 ml of ethanol and 2.0g of naphthalene - 1,5 - disulphonic acid are added. Heating is effected for a short time until all has dissolved and it is then allowed to cool down, whereupon the neutral naphthalene - 1,5 - disulphonate crystallizes out. This melts at 280—281° after recrystallizing from methanol.

EXAMPLE 9:

α - 3 - chloro - 5 - [(1' - allyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene

3.25g of α - 3 - chloro - 5 - (2' - piperidyl - methylene) - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene, 0.39g of powdered sodium amide and 30 ml of absolute toluene are boiled under reflux for 15 hours. The mixture is then cooled to room temperature and a solution of 1.21g of allyl bromide in 5 ml of toluene added, stirred for one hour and then boiled under reflux for one hour. After cooling, the solution is washed twice with water and then the basic substances extracted three times with 5% acetic acid. The acid extract is then rendered alkaline with sodium hydroxide solution and the precipitated bases taken up in ether. After drying over potassium carbonate, the volume is reduced by evaporation and the residue is dissolved in acetone, whereupon some starting material remains behind in crystalline form.

In order to remove the starting material completely, the acetone mother liquor is reduced in volume once more, the residue is dissolved in 20 ml of benzene and the solution boiled under reflux during 20 minutes after adding 1g of maleic acid anhydride. 1 ml of methanol is then added, boiling repeated for a further 5 minutes, dilution effected by adding 50 ml of hexane, a solution of 3g of triethanolamine in 50 ml of water added and shaken thoroughly. The organic phase which separates is washed twice more with water, then dried over potassium carbonate and reduced in volume. The residue is distilled in a bulb tube, whereupon a colourless oil distils over at 170—180° (air bath temperature) at 0.02 mm Hg.

1g of this oil and 396 mg of naphthalene - 1,5 - disulphonic acid are dissolved in 10 ml of boiling ethanol. On cooling the solution, the neutral naphthalene - 1,5 - disulphonate crystallizes. It melts from methanol at 294—296° with decomposition.

EXAMPLE 10:

α - 3 - chloro - 5 - [1' - (2'' - hydroxyethyl) - piperidyl - 2' - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene

3.25g of α - 3 - chloro - 5 - (2' - piperidyl - methylene) - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene, 35 ml of ethanol and 19 ml of 4.8% ethanolic ethylene oxide solution are heated for 1 hour to 85° in a bomb

tube and the solution subsequently reduced in volume by evaporation. The residual froth is dissolved in 15 ml of ethanol and 1.4g of naphthalene - 1,5 - disulphonic acid added to the solution, whereupon the neutral naphthalene - 1,5 - disulphonate crystallizes after a short time. It melts at 242—244° after recrystallization from ethanol.

EXAMPLE 11:

3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 5H - dibenzo[a,d]cycloheptene

a) 3 - chloro - 5 - (pyridyl - 2' - methyl) - 5H - dibenzo[a,d]cyclohepten - 5 - ol

9.5g of 2-methylpyridine is added dropwise to an ethereal lithium phenyl solution, prepared from 1.4g of lithium and 15.7g of bromobenzene. The solution is left to boil under reflux during 30 minutes, cooled down to 20° and a total of 12.02g of finely powdered 3 - chloro - 5H - dibenzo[a,d]-cyclohepten - 5 - one added in portions. After stirring for one hour at room temperature, the solution is poured into 200 ml 10% aqueous ammonium chloride solution and extraction effected repeatedly with methylene chloride. After drying over sodium sulphate, the solvent is removed by evaporation and the residue crystallized from ethanol. M.p. of the 3 - chloro - 5 - (pyridyl - 2' - methyl) - 5H - dibenzo[a,d]cyclohepten - 5 - ol = 121—122°.

b) 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol

9.8g of 3 - chloro - 5 - (pyridyl - 2' - methyl) - 5H - dibenzo[a,d]cyclohepten - 5 - ol, 4.39 ml of dimethyl sulphate and 50 ml of acetone are boiled for 2.5 hours under reflux. The 3 - chloro - 5 - [(1' - methyl - pyridinium - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol - methyl sulphate which crystallizes upon cooling, is filtered off, dried, dissolved in 60 ml of methanol and the solution shaken with hydrogen after adding 0.3g of platinum dioxide, until the calculated amount of hydrogen has been taken up. The catalyst is then filtered off, the solution reduced in volume by evaporation and the residue shaken with dilute sodium hydroxide and methylene chloride. The methylene chloride phase is separated, dried over sodium sulphate, reduced in volume by evaporation and the residue crystallized from ethanol. The resulting isomeric mixture of 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol melts at 148—155°.

c) 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 5H - dibenzo[a,d]-cycloheptene

The solution of 11g of 3 - chloro - 5 - [1' - methyl - piperidyl - 2') - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol in 55 ml of glacial acetic acid is saturated with gaseous hydrogen chloride. 9 ml of acetic anhydride are added, the solution heated to 100° for 2 hours and reduced in volume by evaporation in a vacuum. The residue is dissolved in water, the solution rendered alkaline with potassium hydroxide while cooling, and extracted several times with methylene chloride. After drying over potassium carbonate and evaporating the solvent, the residue is taken up in hexane, the insoluble remains are filtered off and the solution again reduced in volume by evaporation. The residue is dissolved in ethanol, the solution is adjusted to pH4 with hydrobromic acid, again reduced in volume in a vacuum and the residual froth dissolved in acetone, from which the hydrobromide of 3 - chloro - 5[(1' - methyl - piperidyl - 2') - methylene] - 5H - dibenzo-[a,d]cycloheptene crystallizes. This melts at 190—195° (decomp.) after recrystallizing from ethanol/ether.

The acetone mother liquor of the hydrobromide of the β-isomer is reduced in volume once more, the residue dissolved in water, the solution rendered alkaline with potassium hydroxide solution and shaken out with methylene chloride. After drying over potassium carbonate and evaporating the solvent, the residue is dissolved in hexane, whereupon the α-isomer of the compound quoted in the title crystallizes. M.p. = 120—121° after twice recrystallizing from hexane.

EXAMPLE 12:

3 - chloro - 5 - [1' - (1'' - methyl - piperidyl - 2'') - ethylidene] - 5H - dibenzo[a,d]cycloheptene

a) 3 - chloro - 5 - [1' - (pyridyl - 2'') - ethyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol

10.5g of α-ethylpyridine are added dropwise to an ethereal solution of lithium phenyl, prepared from 1.4g of lithium and 15.7g of bromobenzene. After boiling under reflux for 30 min. and cooling to 20°, a solution of 12.12g of 3 - chloro - 10,11 - dihydro - 5H - dibenzo[a,d]cyclohepten - 5 - one in 35 ml of ether is added dropwise. Stirring is effected for a further hour at room temperature, the solution is poured into 200 ml of 10% aqueous ammonium chloride solution and extracted several times with methylene chloride. After drying over sodium sulphate, the solvent is evaporated and the residue taken up in methanol, whereupon a diastereoisomeric mixture of the compound quoted

in the title crystallizes. M.p. = 110—116° after recrystallizing from methanol.

b) 3 - chloro - 5 - [1′ - (1″ - methyl - pyridinium - 2″) - ethyl] - 5H - dibenzo-[a,d]cyclohepten - 5 - ol - methyl sulphate

23g of 3 - chloro - 5 - [1′ - (pyridyl - 2″) - methyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol, 8.2 ml of dimethyl sulphate and 100 ml of acetone are boiled under reflux for 8 hours, whereupon the quaternary salt commences to crystallize after approximately 3 hours. After standing the solution, the salt mixture is filtered off, washed thoroughly with acetone and dried in the vacuum desiccator. M.p. 145—155° (decomp.).

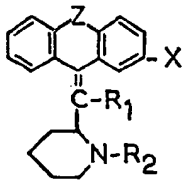
c) 3 - chloro - 5 - [1′ - (1″ - methyl - piperidyl - 2″) - ethylidene] - 5H - dibenzo[a,d]cycloheptene

The solution of 16.3g of 3 - chloro - 5 - [1′ - (1″ - methyl - pyridinium - 2″) - ethyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol - methyl sulphate in 150 ml of methanol is shaken with 0.5g of platinum oxide in a hydrogen atmosphere, whereupon 3 mol of hydrogen are taken up. When absorption of hydrogen has ceased, the catalyst is removed by filtering, the solution is reduced in volume, the residue shaken with dilute sodium hydroxide solution and methylene chloride, the methylene chloride phase separated, dried over potassium carbonate and reduced in volume by evaporation. The resinous residue consists of a diastereoisomeric mixture of 3 - chloro - 5 - [1′ - (1″ - methyl - piperidyl - 2″) - ethyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ols, from which a component having a melting point of 151—153° may be obtained in pure form by crystallization from methanol or acetone.

The crude diastereoisomeric mixture is dissolved in 60 ml of glacial acetic and the solution saturated with gaseous hydrogen chloride. 9.5 ml of acetic anhydride are then added, boiled for 5 hours under reflux and reduced in volume by evaporation in a vacuum. The residue is dissolved in water, the solution rendered alkaline with sodium hydroxide solution, extracted with methylene chloride and the solvent evaporated after drying over potassium carbonate. The resin which remains is dissolved in ethanol and the calculated amount of naphthalene - 1,5 - disulphonic acid for producing the neutral naphthalene - 1,5 - disulphonate added, while heating. On cooling a mixture of 3 - chloro - 5 - [1′ - (1″ - methyl - piperidyl - 2″) - ethylidene] - 5H - dibenzo[a,d]cycloheptene - naphthalene - 1,5 - disulphonates crystallizes. M.p. approx. 265—275° (decomposition).

WHAT WE CLAIM IS:—

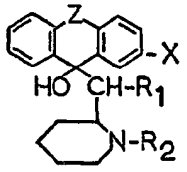
1. A process for the production of 5 - [1′ - (piperidyl - 2″) - alkylidene] - 5H - dibenzo[a,d]cycloheptenes of the formula I,



I

in which Z denotes a $-CH_2-CH_2-$ or a $-CH=CH-$ radical,
X denotes a hydrogen, fluorine, chlorine or bromine atom,
R_1 denotes a hydrogen atom or an alkyl (C_1—C_3) radical, and
R_2 denotes a hydrogen atom or an alkyl (C_1—C_4), alkenyl (C_2—C_4) or 2-hydroxyalkyl (C_2 or C_3) radical,

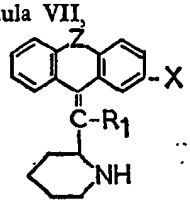
which comprises heating with a strong acid or acid anhydride to split off the elements of water from a compound of the formula II,



II

in which Z, X, R_1 and R_2 have the above significance.

2. A process for the production of those of the compounds of formula I, wherein R_2 denotes an alkyl (C_1—C_4) or alkenyl (C_2—C_4) radical, characterized in that a compound of the formula VII,



VII

in which Z, X and R_1 have the significance stated in Claim 1, is alkylated in the presence of a basic catalyst with a compound of the formula VIII,

R_2'—Halogen VIII

in which R_2' denotes an alkyl (C_1—C_4) or alkenyl (C_2—C_4) radical.

3. Modification of the process according to Claim 2, in which a compound VII defined in Claim 2 is acylated with a reactive derivative of an acid of the formula IX,

$$R_3COOH \qquad IX$$

in which R_3 denotes an alkyl or alkenyl radical containing one $-CH_2-$ radical less than R_2,

and the resulting acid amide is reduced with lithium aluminium hydride or diborane.

4. Modification of the process according to Claim 2, in which, when it is desired to produce those compounds I defined in Claim 1 having a radical R_2 = methyl, a compound VII defined in Claim 2 is reacted with formic acid and formaldehyde.

5. A process for the production of those compounds of formula I, wherein R_2 denotes a 2-hydroxyalkyl (C_2 or C_3) radical, characterised in that a compound VII defined in Claim 2 is reacted with the corresponding epoxide.

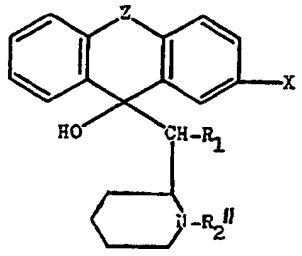
6. A process for the production of the compounds of the formula I defined in Claim 1, substantially as herein described with reference to any one of the Examples.

7. A process for the production of the acid addition salts and quaternary ammonium compounds of the compounds of formula I defined in Claim 1, which comprises reacting a compound I defined in Claim 1 with an organic or inorganic acid or a quaternization agent.

8. The compounds of formula I defined in Claim 1, whenever produced by the process claimed in any one of Claims 1—6.

9. The acid addition salts and quaternary ammonium compounds of the compounds of formula I defined in Claim 1, whenever produced by the process claimed in Claim 7.

10. A process according to Claim 1, in which there is used as starting material a 5 - [1′ - (piperidyl - 2″) - alkyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol of the formula IIa,



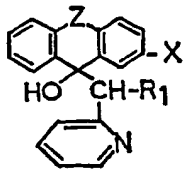
IIa

in which Z denotes a $-CH_2-CH_2-$ or a $-CH=CH-$ radical,

X denotes a hydrogen, fluorine, chlorine or bromine atom, R_1 denotes a hydrogen atom or an alkyl (C_1—C_4) radical, and

R_2'' an alkyl (C_1—C_4) or 2-hydroxyalkyl (C_2—C_3) radical,

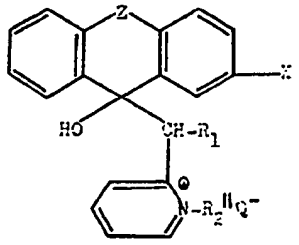
and the last mentioned compound is produced by quaternizing a compound having the formula III,



III

in which Z, X and R_1 have the above significance,

and then reducing catalytically with a platinum or Raney nickel catalyst the resulting compound of formula IVa

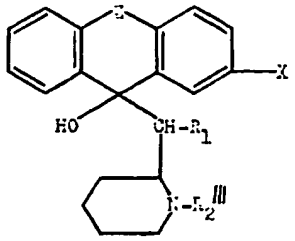


IVa

in which Z, X, R_1 and R_2'' have the above significance, and

Q^- denotes the anion of the quaternization agent.

11. A process according to Claim 1, in which there is used as starting material a 5 - [1′ - (piperidyl - 2″) - alkyl] - 5H - dibenzo[a,d]cyclohepten - 5 - ol of the formula IIb,



IIb

in which Z denotes a $-CH_2-CH_2-$ or $-CH=CH-$ radical,

X denotes a hydrogen, fluorine, chlorine or bromine atom,

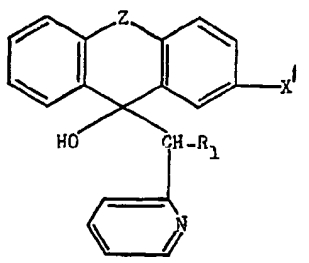
R_1 denotes a hydrogen atom or an alkyl (C_1—C_4) radical, and

R_2''' a hydrogen atom,

and the last mentioned material is produced by reducing catalytically with a platinum

or Raney nickel catalyst or with sodium in absolute ethanol a compound of the formula III defined in Claim 10.

12. A process according to Claim 10, in which there is used as starting material a 5 - (2' - pyridyl - methyl) - 5H - dibenzo-[a,d]cyclohepten - 5 - ol of the formula III*a*,



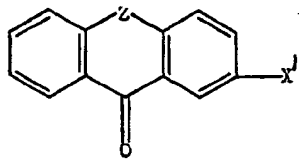
III*a*

in which Z denotes a $-CH_2-CH_2-$ or a $-CH=CH-$ radical,

R_1 denotes a hydrogen atom or an alkyl (C_1—C_4) radical

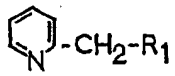
and X' denotes a hydrogen, chlorine, fluorine or bromine atom, with the proviso that X' must be a fluorine or bromine atom when R_1 signifies a hydrogen atom,

and the last mentioned compound is produced by reacting a compound of the formula V*a*,



V*a*

in which Z and X' have the above significance, with a sodium or lithium derivative of a compound of the formula VI,



VI

in which R_1 has the above significance, and hydrolysing the resulting complex compound.

13. A process according to Claim 12, in which the 3 - halogeno - 5H - dibenzo-[a,d]cyclohepten - 5 - one of the formula V*a* defined in Claim 12 is produced by reducing the corresponding *p* - halogenobenzalphthalide with red phosphorus and hydroiodic acid and then effecting intramolecular cyclisation of the resulting *o* - (*p* - halogenophenethyl) - benzoic acid.

14. The compounds of formula I defined in Claim 1 whenever produced by the process claimed in any one of Claims 10 to 13, their acid addition salts and their quaternary ammonium compounds.

15. The 5 - [1' - (piperidyl - 2'') - alkylidene] - 5H - dibenzo[a,d]cycloheptenes of the formula I defined in claim 1, their acid addition salts and quaternary ammonium compounds.

16. 5 - [1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene.

17. 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

18. 5 - [(1' - methyl - piperidyl - 2') - methylene] - 5H - dibenzo[a,d]cycloheptene.

19. 3 - fluoro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

20. 3 - bromo - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

21. 3 - chloro - 5 - (2' - piperidyl - methylene) - 10,11 - dihydro - 5H - dibenzo-[a,d]cycloheptene.

22. 3 - chloro - 5 - [(1' - ethyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

23. 3 - chloro - 5 - [(1' - allyl - piperidyl - 2') - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

24. 3 - chloro - 5 - [1' - (2'' - hydroxyethyl) - piperidyl - 2' - methylene] - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene.

25. 3 - chloro - 5 - [(1' - methyl - piperidyl - 2') - methylene] - 5H - dibenzo-[a,d]cycloheptene.

26. 3 - chloro - 5 - [1' - (1'' - methyl - piperidyl - 2'') - ethylidene] - 5H - dibenzo-[a,d]cycloheptene.

27. Pharmaceutical compositions containing, in addition to a physiologically acceptable carrier, a compound of formula I defined in Claim 1, and/or a physiologically acceptable acid addition salt or quaternary ammonium compound thereof.

for the Applicants:—
G. H. MUNSTER & CO.,
Chartered Patent Agents,
Imperial Buildings,
56, Kingsway, London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.